BIOMIMETICS AND TISSUE ENGINEERING IN THE RESTORATION OF OROFACIAL TISSUES

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P.T.

National Institute of Dental Research
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: September 5, 1998
Application Receipt Date: November 19, 1998

PURPOSE

The National Institute of Dental Research (NIDR) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), invite applications in support of both design directed and hypothesis driven research whose aim it is to develop natural and novel approaches for the repair, restoration, and replacement of oral, craniofacial, dental, skin and musculoskeletal tissues and organs based on a comprehensive scientific understanding of biological structures and their function. The overall goal of this Request for Applications (RFA) is to facilitate multidisciplinary research aimed at development of a new generation of natural and synthetic oral, craniofacial dental and skin/musculoskeletal biomaterials, including total biological approaches for use in instances in which synthetic implants historically have been used. Because of the nature of biomimetics and tissue engineering research, the NIDR and the NIAMS are particularly interested in supporting research conducted by collaborative, interdisciplinary teams of scientists from the fields of engineering, chemistry, physics, mathematics, and biology.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000", a PHS led national activity for setting priority areas. This RFA, Biomimetics and Tissue Engineering in the Restoration of Orofacial Tissues, is related to the priority areas oral health. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock 017-001-

00474-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments and eligible agencies of the Federal government. Collaborative projects with foreign scientists conducting unique research on biomimetics and tissue engineering are encouraged. Also encouraged are applications that include investigators who are racial/ethnic minority individuals, women and persons with disabilities. Although an application must be submitted from a single institution, collaborative arrangements with other institutions are strongly encouraged.

MECHANISM OF SUPPORT

Traditional research project grants (R01), and exploratory/developmental grants (R21) may be submitted in response to this RFA. The R21 awards will be utilized to support highly innovative exploratory studies for which extensive preliminary results may not be available. Through this mechanism investigators can explore new innovative research paradigms. Applicants for the R21 must limit their requests to $100,000 in direct costs per year for two years. R21 grants are not renewable, but future project continuation is possible through other grant mechanisms, such as the R01.

Applications for R01 grants may request up to five years of support. This RFA is a one-time solicitation.

Because of the nature of research involving biomimetics and tissue engineering, the Institutes encourage interdisciplinary collaborative research. In the case of collaborative research projects, a group of investigators may simultaneously submit a minimum of 3 and no more than 5 applications. Collaborative projects with a common theme may be from a single institution or several institutions, may include shared resources, and must demonstrate the interdependence of the individual components. All applications, both collaborative and individual, must provide evidence that the research will be multidisciplinary in nature and applicants are encouraged to specify how the research will further the missions of the NIDR and/or the NIAMS. The maximum total costs for the first year of a group of collaborative projects is $1 million.

It is anticipated that support for this program will begin in FY 2000. Administrative adjustments in project period and/or amount may be required at the time of the award.

FUNDS AVAILABLE

Pending receipt of sufficient numbers of highly scientifically meritorious applications, the NIDR will allocate approximately $4 million in total costs to support projects from this RFA during FY 2000. Although the NIAMS has an interest in collaborative projects for this RFA only, NIAMS will allocate $400,000 in direct costs (approximately $600,000 in total costs) for FY 2000 to support 2 to 3 individual R01s, provided the applications are of high scientific merit. It is possible that a collaborative project in a topic area that overlapped the interests of NIDR and NIAMS could be co-funded by these two Institutes if the project is of high scientific merit. Although this program is provided for in the financial plans of the NIDR and NIAMS, the award of grants pursuant to this RFA is contingent upon the receipt of a sufficient number of high quality applications and the availability of funds for this purpose. Policies that govern research grant programs of the NIH will prevail.

RESEARCH OBJECTIVES

Background

Over the last few years biomimetics and tissue engineering have emerged as a new vision in the field of tissue and organ repair and restoration. Biomimetics and tissue engineering are interdisciplinary fields that combine information from the study of biological structures and their functions with physics, mathematics, chemistry and engineering for the generation of new materials, tissues and organs. These approaches can offer new ways of: (a) developing biological solutions for future design and synthesis of composite materials such as bone, cartilage, tendon, ligament, skin, dentin, enamel, cementum and periodontal ligament; (b) replacing and assembling functional tissues and organs; and (c) evaluating medical and dental implants.

In the area of craniofacial, oral and dental principles from biomimetics and tissue engineering are applied to developing dental and facial implants, new polymers for guided tissue regeneration used in treating periodontal disease and bone and connective tissue defects, coral-based hydroxyapatite replicas for reconstruction of alveolar ridges and other osseous defects, temporomandibular joint (TMJ) and other joint prostheses, formation of bone matrix substitutes, and artificial replicas of bone, skin, and mucosa.

Rationale

There is a need to develop the next generation of restorative materials and medical implants. New avenues of scientific inquiry may enable the development of biomaterials that are safe, reliable, "smart", long-lasting, and perform ideally in their respective biological environments. In order to determine how best to facilitate development in the areas of biomimetics and tissue engineering, the National Institute of Dental Research convened a 2-day workshop entitled "Biomimetics, Tissue Engineering and Biomaterials" on September 24-26, 1996 which brought together experts in the fields of biomaterials, biomimetics, tissue engineering, cellular and molecular biology as well as representatives from several NIH Institutes, other federal agencies and industry. These experts were charged with developing recommendations that would provide a foundation for a research program in those areas having specific application to the mission of the Institute. This RFA is issued in accordance with the recommendations of workshop participants' along with those of the National Advisory Dental Research Council (NADRC).

One intent of this RFA is to encourage and promote multidisciplinary research on tissue engineering and biomimetics in the development of biomedical implants as they apply to the repair, regeneration and maintenance of craniofacial, oral and dental tissues and structures. Applicants for both individual and collaborative projects are therefore encouraged to include teams of individuals whose expertise broadens the scope of the scientific approach of the team. An additional intent of the RFA is to encourage new investigators to enter this area of research. These may be senior investigators who have no previous experience in this field, or scientists from any field who are at the beginning stages of their research careers. Applicants are encouraged to include either category of new investigator on their research team. In addition, applications are encouraged from new investigators of either category.

Objective and Scope

The following research topics are provided as examples. They are not listed in any priority order and are not intended to be inclusive or restrictive.

o development and/or refinement of methods for the exploration and evaluation of the dynamic natural state of tissues and cells (i.e., mechanisms and timing of cell fate, cell spatial orientation) and of hierarchical levels of craniofacial, oral and dental tissues and organs for the design and development of new biologically-based materials;

o development of methodologies and molecular probes to digitally record and track events during craniofacial, oral and dental normal embryogenesis, and diseases states; and development of virtual models of cellular and tissue behavior to enable testing of theories before in vitro and in vivo assessments;

o development of methodologies for accurate protein and cellular positioning on biomaterial matrices, and development of biopolymers with the ability to deliver signals to cells within the interstices of three dimensional matrices;

o design of matrices that would promote the formation of facial musculature, neurological pathways, bone, connective tissues, and skin for use in the repair of orofacial tissues and musculoskeletal tissues;

o development of practical systems for site-specific targeting (i.e., salivary glands, oral epithelium, tooth apparatus) of cells, genes and/or drugs;

o advancement of the fundamental knowledge of biomineralization including biomineralization precursor phases, microstructure formation, templating growth and morphogenesis of bone and teeth, and development of effective substitutes or replacements for these structures;

o development of effective biomimetic routes to enhance the function of the oral soft and hard tissues and salivary glands which may be lost due to acquired or congenital abnormalities;

o development of research strategies to advance the understanding of the mechanisms of repair and maintenance of intraoral soft tissue injury and engineering of artificial oral soft tissues;

o development of artificial salivary glands through studies which include identification of salivary stem cells, cell-based therapies, and synthesis of appropriate classes of matrix materials that support the physiology of a salivary secretory cell;

o establishment of novel approaches to promote nerve outgrowth, through the improvement of models at the organ/tissue level as well as at the molecular level;

o transplantation of undifferentiated genetically modified cells and gene-based therapies to assist nerve cells to regenerate;

o development and use of high resolution imaging techniques to evaluate the interfaces between biomimetically derived biomaterials and their biological environment (i.e., enamel, dentin, cementum, bone, periodontal and other ligaments); and

o development of measurement systems that will evaluate short- and long-term safety, efficacy, utility, economy and applicability of biomimetic and tissue engineering-based materials.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects of the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998. All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

LETTER OF INTENT

Prospective applicants are asked to submit, by September 5, 1998, a letter of intent that includes a descriptive title of the overall proposed research, the name, address and telephone number of the Principal Investigator(s), the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains is helpful in planning for the timely review of the applications. It helps NIDR and NIAMS staff to estimate the potential review workload and to avoid possible conflicts of interest in the review.

The letter of intent is to be addressed to Dr. Eleni Kousvelari at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Prospective applicants are encouraged to communicate with program and grants management staff of the sponsoring Institutes as early as possible in the planning phase of application preparation. Advice and suggestions by staff may materially assist applicants to ensure that the objectives and structure and the budget format are acceptable. Applicants are also encouraged to obtain a copy of the NIDR workshop report either from the NIDR Home Page (http://www.nidr.nih.gov) or from Dr. Eleni Kousvelari at the address listed under INQUIRIES.

The research grant application form PHS 398 (rev. 5/95) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: GrantsInfo@nih.gov. The forms are also available on the NIH homepage at http://grants.nih.gov/grants/funding/phs398/phs398.html.

The RFA label available in the PHS 398 application form kit must be affixed to the bottom of the face page of the original and the original must be placed on top of the entire package. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, in order to identify the application as a response to this RFA, the RFA title (Biomimetics and Tissue Engineering in the Restoration of Orofacial Tissues) and number (DE-98-009) must be typed in item 2 of the face page of the application form and the YES box must be checked.

Applicants from institutions that have a General Clinical Research Centers (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

Submit a signed, typewritten original of the application, including a cover letter, the checklist and three signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must also be sent to:

Dr. George Hausch
Scientific Review Section
Division of Extramural Research
National Institute of Dental Research
Natcher Building, Room 4AN-38D
Bethesda, MD 20892-6402

Applications must be received by November 19, 1998. If an application is received after that date, it will be returned to the applicant without review.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the Center for Scientific Review (CSR) and responsiveness by the NIDR and NIAMS. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive will be evaluated for scientific and technical merit by an appropriate peer review group convened by the sponsoring Institutes. As part of the initial merit review, a process will be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other applications received in response to the RFA. Applications judged to be competitive will be discussed and be assigned a priority score. Applications determined to be non-competitive will be withdrawn from further consideration and the Principal Investigator and the official signing for the applicant organization will be notified. Applications will receive a secondary level of review by NIDR's and NIAMS' Advisory Council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score and weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

Investigator: Is the investigator appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

Collaborative research: Is the degree to which the project will represent collaborative research among investigators from different disciplines within an individual R01 acceptable? Is the work proposed among individual R01s interdisciplinary in nature? Is the likelihood of effective collaboration among the investigators? What is the likelihood that the proposed research will advance the knowledge in tissue engineering, biomimetics, and biomaterials for application to craniofacial, oral and dental health?

Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the

scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The R21 mechanism encourages applications to explore new research paradigms in biomimetics, and tissue engineering as applied to the objectives of this RFA. In the case of R21 applications, comprehensive preliminary results demonstrating feasibility are not required. It is, however, incumbent on the applicant to provide a convincing rationale for the proposed studies and to relate them to the focus of this RFA.

The availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries that are not readily available in the United States or that provide augmentation of existing U.S. resources will be considered in the review.

The initial review will also examine the appropriateness of proposed budget and duration, the adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research and plans for the recruitment and retention of subjects, the provisions for the protection of human and animal subjects, and the safety of the research environment.

AWARD CRITERIA

The earliest anticipated date of award is December 1999. Applicants should be aware that, in addition to scientific merit, program priorities and program balance, the total cost of the proposed project and the availability of funds will be considered in making funding recommendations. In addition, complementary funding from other public and private sources including foundations and industrial concerns is encouraged. In circumstances in which applications have similar scientific merit, but vary in cost competitiveness, the more cost competitive application is likely to be selected for funding.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Dr. Eleni Kousvelari
Division of Extramural Research
National Institute of Dental Research
Natcher Building, Room 4AN 18A
Bethesda, MD 20892-6402
Telephone: (301) 594-2427
FAX: (301) 480-8318
Email: kousvelari@de45.nidr.nih.gov

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS 37K
Bethesda, MD 20892-6500
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: panagisj@ep.niams.nih.gov

Direct inquiries regarding grants management issues to:

Mr. Kevin Crist
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Natcher Building, Room 4AS 55
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Telephone: (301) 594-4800
FAX: (301) 480-8301
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Ms. Vicki Maurer
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Schedule

Letter of Intent Receipt Date: September 5, 1998
Application Receipt Date: November 19,1998
Scientific Review: April/May 1999
Advisory Council Date: September/October 1999
Earliest Award Date: December 1999

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. Nos. 93.121 and 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children.

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